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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

HED DOC. NO.

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **September 5, 2000**

MEMORANDUM

SUBJECT: ***MALATHION:*** **REVISED** Responses to Registrant's Comments

FROM: Yung G. Yang, Ph.D. Yung G. Yang 9/5/00
Toxicology Branch 1
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 9/5/00
and
Elizabeth Doyle, Co-Chair E.A. Doyle 9/5/00
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Paula Deschamp, Risk Assessor
Reregistration Branch II
Health Effects Division (7509C)

PC Code: 057701 **Registrant: Cheminova Agro**

On August 15, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed comments submitted by the Registrant entitled "Comments from Cheminova A/S on EPA's preliminary risk assessments for Malathion". The HIARC's responses and conclusions are presented in this report.

NOTE: This report was revised to correct the NOAEL for the chronic dietary and long-term dermal risk assessment (the correct dose is 2.4 mg/kg/day). This is the only change made to the report.

Committee Members in Attendance

Members present were: William Burnam, Pamela Hurley, Tina Levine, Jess Rowland, Elizabeth Mendez, David Nixon, Jonathan Chen, and Ayaad Assaad

Member(s) in absentia: Elizabeth Doyle, Yung Yang, and Brenda Tarplee

Data evaluation prepared by: Yung Yang, Toxicology Branch 1

Also in attendance were: Brian Dementi, Alberto Protzel, and Paula Deschamp.

Data Evaluation / Report Presentation: Mike Ioannou, TOX1

Background

On November 6, 1997, the HIARC evaluated the toxicology data base, selected doses and endpoints for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments, and addressed the sensitivity of infants and children from exposure to Malathion as required by the Food Quality Protection Act (FQPA) of 1996. Following that meeting, the Agency pursued the external peer review mechanism to address a number of issues raised by Dr. Brian Dementi. The external peer review panel submitted their responses to the Agency in May, 1998. On August 18, 20 and 27, 1998, the HIARC evaluated the comments and responses provided by the review panel (Memorandum from J. Rowland to D. Locke, Dated December 22, 1998).

On July 10, 2000, the Registrant (Cheminova A/S) submitted a response entitled "Comments from Cheminova A/S on EPA's preliminary risk assessments for Malathion". On August 15, 2000, the HIARC evaluated the Registrant's response. The HIARC's decisions are presented in this report.

Issue #1. 90-day feeding study in dogs

Registrant's Comment: The Registrant (Cheminova) believes that a 90-day feeding study in dogs is not needed because available data from a one-year dog toxicity study (using six animals/sex/group) and a 28-day dog toxicity study (using three animals/sex/group) provide adequate information on the toxicity of Malathion in non-rodent species.

HIARC's Response: The HIARC re-affirmed its previous conclusion that a NOAEL was not established in the one-year dog study. The endpoint of plasma and RBC ChE I (cholinesterase inhibition) at LOAEL of 62.5 mg/kg/day was based on biological significance and not on statistical significance. Also, the HIARC questioned the validity of the ChE I methodology used in that study. For the 28-day oral (capsule) toxicity study in Beagle dogs (MRID 45077703), a preliminary report indicated that this 28-day dog study may have served initially as a range-finding study for the chronic study. This study standing alone, or considered in conjunction with the chronic study, does not address the concern for establishing a no adverse effect level for RBC or plasma ChE I in the dog which was one of the concerns expressed previously by the HIARC.

Conclusion: The HIARC concludes that a 90-day feeding study in the dog is required. This conclusion was based on the following reasons: (1) ChE I showed a shallow dose-response in the chronic dog study; the NOAEL in the dog could be lower than the dose (chosen from a rat study) used presently for risk assessment, (2) the conduct of the study should be by the dietary route of exposure which is more appropriate than the capsule used in the previous study, and (3) an up-to-date methodology should be used to measure ChE I.

Issue #2. 90-day inhalation toxicity study in rats

Registrant's Comment: The Registrant (Cheminova) is considering conducting a new study using a tiered approach to define a NOAEL for nasal histopathology for the short- and intermediate-term inhalation exposure risk assessments. The study will be designed to demonstrate reversibility of any effects. Also, Cheminova believes that in a previously conducted 90-day inhalation toxicity study (Beattie 1994), a clear NOEL for cholinesterase inhibition was achieved at 0.1 mg/L -- the lowest dose tested.

HIARC's Response: The HIARC concurred with the Registrant that a NOAEL has been established in the 90-day inhalation study in rats (MRID 43266601) at 0.1 mg/L based on lack of statistical significance and the degree of inhibition could be within background level due to high variability. Although a NOAEL has been established, ChE I data are still required in the new study since this new study is nose-only exposure which is different from the 1994 study (whole body exposure).

Conclusion: The HIARC concludes that a new 90-day inhalation study (nose only) is required as indicated in the previous HIARC report. The study should follow the Guideline 870.3465 protocol with measurements of ChE I and nasal histopathology. The DER of the 90-day inhalation study (MRID 43266601) should be revised to indicate that a NOAEL has been established at 0.1 mg/L for plasma and RBC ChE I. Also, it is to be indicated that a NOAEL still has not been established for the nasal lesions. A MOE of 1000 is required for short, intermediate, and long-term occupational/ residential inhalation risk assessments based on the lack of NOAEL and the severity of the observed nasal lesions.

A revised table for the doses, toxicology endpoints selected and Margins of Exposure (MOE) dietary and non-dietary exposure assessments is attached.

A summary of the doses, toxicology endpoints selected and Margins of Exposure (MOE) dietary and non-dietary exposure assessments are tabulated below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	UF/ MOE
Acute Dietary	NOAEL =50.0	Maternal toxicity	Range-Finding & Main Developmental toxicity studies - rabbits	UF =100
Chronic Dietary	NOAEL=2.4	Inhibition of plasma cholinesterase activity	Combined/Chronic Toxicity Carcinogenicity - Rat	UF = 100
Short-Term (Dermal)	NOAEL =50.0	Inhibition of plasma, RBC and brain cholinesterase activity	21-Day Dermal - Rabbit	MOE =100
Intermediate-Term (Dermal)	NOAEL=50.0	Inhibition of plasma, RBC and brain cholinesterase activity	21-Day Dermal - Rabbit	MOE= 100
Long-Term (Dermal)	NOAEL=2.4	Inhibition of plasma cholinesterase activity	Combined/ Chronic Toxicity - Rat	MOE = 100
Short-Term (Inhalation)	LOAEL= 0.1 mg/L	Histopathology in respiratory epithelium	90-Day Inhalation Toxicity	MOE = 1000[a]
Intermediate-Term (Inhalation)	LOAEL= 0.1 mg/L	Histopathology in respiratory epithelium	90-Day Inhalation Toxicity	MOE= 1000[a]
Long-Term (Inhalation)	LOAEL= 0.1 mg/L	Histopathology in respiratory epithelium	90-Day Inhalation Toxicity	MOE= 1000[a]

a = A MOE of 1000 is required (includes the conventional 100 and an additional 10x for the use of a LOAEL and the severity of the nasal lesions observed in the two-week range finding study).